REMARKS

Claims 19-36 are pending. Claims 19 and 32-36 have been amended. Support for the amendment to claims 19, 35, and 36 can be found throughout the specification as filed, e.g., at page 10, lines 22-23, and at page 1, lines 30-31.

Rejections Under 35 U.S.C. § 102

Claims 19-20, 23, and 24-34 are rejected as anticipated by Chavin et al. ("Chavin"). The Examiner states

> Applicant's 'instructions' represent an intended use of the immunosuppressive agent and do not add any structural limitations to the kit as a whole or the immunosuppressive agents listed...Furthermore, instructions as to the use of a product are not given patentable weight in a product claim where the body of the claim does not depend on the preamble or instructions for completeness, but, instead, the structural limitations are able to stand alone. The MPEP states that 'in apparatus, article, and composition claims, intended use must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art.' In re Casey, 152 USPQ 235 (CCPA 1967); In re Otto, 136 USPQ 458, 459 (CCPA 1963) (MPEP 2111.02).

This rejection is respectfully traversed. As amended, the claims are directed to kits for inducing tolerance to a graft comprising an anti-CD2 antibody or antigen-binding fragment thereof in a pharmaceutically acceptable carrier, an immunosupressive agent, and instructions to administer the anti-CD2 antibody or antigen binding fragment thereof and to administer a short course of the immunosuppressive agent at a high dose to a human subject to induce tolerance.

The claims are not merely composition claims with an "intended use" limitation, as the Examiner states. The claims are clearly not directed to the compositions alone. On the contrary, the presence of specific instructions is a limitation of the claimed kits, as is the presence of the anti-CD2 antibody or antigen-binding fragment thereof, and the immunosuppressive agent. It is axiomatic in patent law that each limitation must be considered in determining the patentability of the claim as a whole, in this case of the claimed kit.

Further, it is well settled that a kit is not a "composition" in terms of patentability, but an article of manufacture. See *In re Venezia*, 530 F. 2d 956, 960 (CCPA 1976), stating "[we] therefore hold that a group or 'kit' of interrelated parts is a 'manufacture' as that term is used in section 101." The Examiner relies on *In re* Casey, 152 USPQ 235 (CCPA 1967) and the MPEP to argue that "instructions as to use of a product are not given patentable weight..." This is an incomplete reading of *In re Casey* and the MPEP. Instead, as noted at MPEP 2115, the line of cases that includes *In re Casey* "is limited to claims directed to machinery which works upon an article or material in its intended use. It does not apply to product claims or kit claims (i.e., claims directed to a plurality of articles grouped together as a kit)." (emphasis added).

As the Examiner is aware, each limitation must be considered in determining patentability of the claim as a whole, and it is incorrect to consider each limitation separately. Furthermore, the law requires that the content of instructions required by a claim be given patentable weight. This is made explicitly clear in *In re Gulack*, 703 F.2d 1381 (Fed. Cir. 1983). *In re Gulack* provides:

> We understand the board as not giving the printed matter patentable weight because the board felt that there is no functional relationship between the printed matter and the substrate. In doing so, we do not interpret the board as holding that the printed matter can be ignored because it, by itself, is non-statutory subject matter. The board cited no authority in analyzing the relevance of the lack of a functional relationship, or of the status of the printed matter as non-statutory subject matter, to its decision not to accord the printed matter patentable weight. Because of the possible ambiguity of the board's articulation of its holding, we feel compelled to clarify the distinction.
>
> Differences between an invention and the prior art cited against it cannot be ignored merely because those differences reside in the content of the printed matter. [FN8] Under section 103, the board cannot dissect a claim, excise the printed matter from it, and declare the remaining portion of the mutilated claim to be unpatentable. The claim must be read as a whole. [FN9] If the board meant to disregard that basic principle of claim interpretation, we must reverse the rejection as a matter of law. (In re Gulack at 1385, emphasis added.)
>
> What is required is the existence of differences between the [claims] and the prior art sufficient to establish patentability. . . .[T]he critical question is whether there

exists any new and unobvious functional relationship between the printed matter and the substrate (In re Gulack at 1386, emphasis added)

In the present application, the instructions have a new functional relationship to the claimed compositions. That is, these instructions specify that an anti-CD2 antibody or antigen binding fragment thereof is to be administered to a human subject, and a short course of the immunosuppressive agent is to be administered to the subject at a high dose.

Chavin does not teach or suggest the claimed kits. As discussed above, the content of the instructions must be considered. Chavin does not teach a combination of an anti-CD2 antibody or antigen binding fragment thereof, an immunosuppressive agent, and instructions for administering the antibody and the agent to a human subject. Chavin discloses administering agents to murine subjects. In addition, Chavin is concerned with the administration of low, subtherapeutic doses of immunosuppressive agents. Chavin does not implement or describe a short course administration of a high dose of an immunosuppressive agent. The claimed kits provide instructions for administering the antibody and immunosuppressive agent at doses which have therapeutic effects, such as the effect of inactivating T cells in a human subject. For the reasons discussed above, Chavin does not teach or suggest all of the elements of the claims, and therefore does not anticipate the claimed invention.

Rejections Under 35 U.S.C. § 103

Claims 21, 22, 35, and 36 are rejected as obvious over WO 94/20619 ("Bazin"), in view of Chavin. The Examiner states that "instructions for use do not change or affect the structural properties of the products claimed."

Applicant respectfully traverses this rejection. As discussed above, the instructions are a limitation of the claimed kits, and each limitation of the claim must be considered in determining the patentability of the kit as a whole. Chavin fails to disclose a kit comprising an anti-CD2 antibody or fragment thereof, an immunosuppressive agent, and instructions to administer a short course of the immunosuppressive agent to a human subject at a high dose. As discussed above, Chavin does not teach or suggest administration to a human subject or that the

immunosuppressive agent be administered as a short course, high dose administration. In fact, Chavin teaches away from the claimed combinations by noting that "several doses of [cyclosporine A] and rapamycin in combination with αCD2 did not prolong survival over αCD2 administered alone." (abstract). One would not have arrived at the claimed compositions from the disclosure of Chavin. Bazin does not make up for these deficiencies of Chavin.

Furthermore, Applicant disagrees with the Examiner's assertion that there is motivation to combine the teachings of Bazin and Chavin. See the Office Action mailed March 27, 2003. Specifically, the Examiner stated that "Based on the motivation provided by Chavin et al. for combining anti-CD2 antibody and FK506 to inhibit graft rejection, it would have been prima facie obvious to the skilled artisan to administer FK506 with the LO-CD2a antibody taught by Bazin et al. in order to effect a synergistic increase in tolerance induction in humans with a reasonable expectation of success." The present claims recite kits wherein the kits provide instructions to administer the immunosuppressive agent at a high dose. Chavin discloses synergy for use of low doses of FK506 only. Chavin also notes that other immunosuppressive agents such as cyclosporine and rapamycin did not provide a synergistic increase in tolerance induction. See, e.g., the abstract of Chavin. Thus, Chavin does not provide the requisite motivation to use a combination of an immunosuppressive agent and an anti-CD2 antibody where the immunosuppressive agent is administered as a short course, high dose administration. For the reasons discussed above, Applicant respectfully request that the Examiner withdraw this rejection.

Rejections Under 35 U.S.C. § 112, second paragraph

Claims 19-36 are rejected as indefinite. First, the Examiner states that "it is unclear whether the instructions provided apply to the kit as a whole or are intended to apply only to the immunosuppressive agent separate from the recited combination." The claims, as amended, are directed to kits comprising an anti-CD2 antibody or antigen-binding fragment thereof in a pharmaceutically acceptable carrier, an immunosupressive agent, and instructions to administer a short course of the immunosuppressive agent to a human subject at a high dose and to administer

the anti-CD2 antibody or antigen-binding fragment thereof to the subject. Thus, the instructions are directed to administration of both the anti-CD2 antibody or antigen-binding fragment thereof, and the immunosuppressive agent.

The Examiner also stated that the term "high dose is a relative term such that the metes and bounds of the claims cannot be determined." This rejection is respectfully traversed. Applicant provides ranges of doses of immunosuppressive agents, methods for determining appropriate dosages, and guidance for administering short courses of these dosages. In view of this disclosure, the meaning of "high dose" can be easily determined by a skilled artisan. See, for example, page 18, lines 20-25, where it states that "in monkeys, a dose of 10 mg/kg cyclosporine with a blood level of about 500-1,000 ng/ml is sufficient to induce tolerance to class II matched class I minor antigen mismatched kidneys. The same blood level, 500-1,000 ng/ml is sufficient to induce tolerance in pigs." See also page 22, lines 8-9, which state that "the suitable dosage in pigs is about 15 mg/kg delivered intramuscularly. The dosage in either animal should be such that a blood level of about 500-1,000 ng/ml is maintained." The application further provides that "the dosage should be sufficient to inactivate thymic or lymph node T cells." Therefore, the meaning of "high" in this context, is clear. Thus, in view of the disclosure of the present application, a "high dose" can be easily ascertained. Applicant asks that the rejection of the claims be withdrawn.

Enclosed is a Notice of Appeal, a Petition for Extension of Time, a $330 check for the Appeal fee, and a $950 check for the Extension of Time fee. Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

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